REMARKS

Prior to this Amendment, claims 1-10 and 17-21 were pending. By this Amendment, claim 17 has been canceled and new claims 28 and 29 added. Thus, claims 1-10, 18-21, 28, and 29 are now pending.

The claims have been amended to recite an "ethyl acetate solvate" of carvedilol. Support for this amendment is found in the specification at page 3, lines 13-29, and page 4, lines 9-24, wherein page 3, lines 23-29, discloses a process for preparing a solvate of carvedilol involving recrystallization from ethyl acetate, providing inherent descriptive support for an ethyl acetate solvate of carvedilol. In addition, page 4, lines 21-24, discloses that the carvedilol solvate Form VI has a DTG thermogram showing a weight loss that equals the expected weight loss corresponding to 2 molecules of ethyl acetate per 3 molecules of carvedilol.

The rejections under 35 U.S.C. §112

Claims 18-21 were rejected for lack of enablement.

The Applicants continue to believe that this rejection is in error, for the reasons that were detailed in the Amendment filed May 30, 2007 and that are set forth below.

The Office Action takes the position that preparing the pharmaceutical composition or dosage forms of claims 18-21 will cause Form VI to convert to the thermodynamically most stable form. See the Office Action, sentence bridging pages 12 and 13: "The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the

metastable state to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure."

Since, according to the Office Action, the specification does not teach how to prevent such a conversion to the most stable form, claim 16 lacks enablement. See the Office Action, page 13: "The specification fails to provide the steps of ensuring that the pharmaceutical compositions will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound."

The specification teaches that the claimed carvedilol Form VI can be formulated into pharmaceutical compositions. See page 6, line 1, to page 9, line 29. Thus, the specification teaches that Form VI will persist after being formulated into pharmaceutical compositions. The burden is on the Office Action to provide evidence or reasoning, not just mere speculation, as to why this teaching of the specification is incorrect. See *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971), where the United States Court of Customs and Patent Appeals stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein .... [emphasis in original]
>
> 439 F.2d at 223, 169 U.S.P.Q. at 369.
>
> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. [italics in original; underscoring added]

439 F.2d at 224, 169 U.S.P.Q. at 370.

The Office Action has not met this burden. It should be noted that claims 18-21 contain no limitations requiring all of the atorvastatin in the composition or dosage forms to be Form VI or requiring Form VI to persist for any particular length of time in the composition or dosage forms. The Office Action cited no evidence to support the premise that all of the Form VI is likely to convert so rapidly and so completely into the most stable form when formulated into a pharmaceutical composition or dosage form that a person skilled in the art could not practice the invention defined in claims 18-21.

The only evidence cited in support of this rejection is Rouhi, Chemical and Engineering News, February 24, 2003, pages 32-35 (Rouhi) and Haleblian et al., 1969, J. Pharm. Sci. 58:911-929 (Haleblian).

Rouhi at most shows that metastable forms tend to, i.e., may possibly, convert to the most thermodynamically stable form. See the Office Action, page 13: "Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32)." Rouhi says nothing about the likelihood, the speed of, or the completeness of, such a conversion.

Haleblian provides evidence in support of the Applicants' position by teaching that conversion may be slow and thus metastable forms may be used in pharmaceutical compositions. See page 913: "For example, phase conversion may be so slow in certain ointment bases that a more soluble metastable form may be safely used. It is entirely possible the use of a more thermodynamically energetic form of the drug may results in a more efficacious therapeutic formulation." See also page 927, left column: "Many minerals (argonite, anatase, brookite, etc.), many drugs (75) (atophane, progesterone, estrone,

marfanil, sulfathiazole, veronal, etc.), and even some important metals (copper, silver, zinc, tin, bismuth, and cadmium) are used daily in the metastable form."

There is nothing in Rouhi or Haleblian that supports the premise that Form VI is likely to convert so rapidly and so completely into the most stable form when formulated into a pharmaceutical composition or dosage form that a person skilled in the art could not practice the invention defined in claims 18-21.

The only reason given in the Office Action for such a proposition is the speculation that if Form VI is subjected to the usual procedures for making pharmaceutical compositions it will convert to other forms. See, e.g., the Office Action, paragraph bridging pages 12 and 13:

> [T]he preparation of pharmaceutical compositions requires, for example, milling, adding excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline from, if in the metastable state to resort back to the most thermodynamically stable form which is the form with the lowest vapor pressure.

Furthermore, Rouhi teaches that the second premise underlying this rejection is wrong. Rouhi teaches that the likely outcome of formulation of a crystalline form, when carried out by those skilled in the art, is that the crystalline form would maintain itself for a reasonable period of time such that the pharmaceutical composition would be useful. This is part of the teachings of Rouhi since one of the main themes in Rouhi is that pharmaceutical companies are actively seeking new crystalline forms of compounds (even metastable forms) in order to formulate these new crystalline forms into pharmaceutical compositions (see page 32, right column; "[M]uch effort is being expended looking for metastable forms of currently marketed drugs whose stable forms have been around for a long time." It would make no

sense for pharmaceutical companies to behave in such a manner if the second premise underlying this rejection were correct.

Furthermore, conversion to the most stable form can be quite slow and less stable crystalline forms can co-exist with the most stable crystalline form. See U.S. Pharmacopia #23, National Formulary #18 (1995), page 1843, entry (941), X-Ray Diffraction[1]:

> Many compounds are capable of crystallizing in more than one type of crystal lattice. At any particular temperature and pressure, only one crystalline form (polymorph) is thermodynamically stable. Since the rate of phase transformation of a metastable polymorph to the stable one can be quite slow, it is not uncommon to find several polymorphs of crystalline pharmaceutical compounds existing under normal handling conditions.

The quotation above shows that the this rejection ignores the fact that, even if conversion to a more stable form occurs, conversion may be "quite slow." In fact, this quotation implies that such "quite slow" conversion is "not uncommon." Thus, the evidence of record indicates that the likely outcome of formulating Form VI into pharmaceutical compositions is that Form VI will persist, at least for a period of time sufficient to provide a useful pharmaceutical composition.

In view of the above, it can be seen that the evidence provided in the Office Action is inadequate to support this rejection. Thus, the Office Action failed to provide "acceptable evidence or reasoning" to support the rejection, as required by *Marzocchi*.

The Office Action appears to read claims 18-21 as including solutions of Form VI where the pharmaceutically acceptable carrier is water. See the Office Action, page 13: "Also, a solution prepared from a specific crystalline form and water would contain the free

[1] This reference was cited in the PTO-892 Form accompanying the Office Action of September 1, 2006.

form of the compound." The Applicants note that claim 18 is directed to a pharmaceutical composition comprising "the crystalline solid of carvedilol" of claim 1 (underscoring added). Claims 19-21 depend from claim 18 and thus also require solid carvedilol Form VI. In view of this, it is respectfully requested that this aspect of the rejection is in error.

The Applicants believe that the above discussion demonstrates that claims 18-21 do not lack enablement. In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1-10 and 17-21 were rejected for lack of written description.

In order to provide an adequate written description, the specification must reasonably convey to the artisan that the inventor had possession of the claimed subject matter. *Fiers v. Revel*, 984 F.2d 1164, 1170, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993). While a patent applicant does not have to describe exactly the subject matter claimed, the description must clearly allow persons of ordinary skill in the art to recognize that the applicant invented what is claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991) (citing *In re Gosteli,* 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989).

In one aspect of this rejection, the Office Action, at page 14, stated that overlays are the most useful method to compare PXRD data and an x-ray diffraction pattern is like a fingerprint. The Office Action then stated (pages 14-15): "[A]pplicant has not provided why the certain peaks found in the claims are the only required peaks in the x-ray diffraction pattern that must match ... nor does the specification provide any direction or guidance as to why certain peaks are the only required peaks in the x-ray data or other data."

As understood, the Office Action is requiring the Applicants to have explained why they chose to define their invention in terms of the PXRD peaks that are recited in the claims.

The Applicants know of no requirement that applicants describe why they defined their invention in the manner claimed. The general rule is that applicants are allowed to define their invention as they see fit. *See In re Chandler*, 319 F. 2d 211, 225, 138 U.S.P.Q. 138, 148 (CCPA 1963): "The right of applicants to freedom of choice in selecting phraseology which truly points out and defines their inventions should not be abridged."

Failing to provide reasons why the claims are defined in a particular manner does not give rise to a lack of written description. The only possible relevant inquiry with respect to written description raised by the Office Action's comments is whether the recitation of the PXRD peaks in the claims would lead one of ordinary skill in the art to doubt that the Applicants possessed or had invented the crystalline form that is being claimed.

The specification clearly conveys to one of ordinary skill in the art that the Applicants possessed and had invented the crystalline forms of atorvastatin that are defined by the PXRD peaks recited in the claims.

It is well established in the art of the analysis of crystalline forms of pharmaceutical compounds that a PXRD pattern is characteristic of a particular crystalline form and is used in the art to distinguish that crystalline form from other crystalline forms. The scientific and patent literature demonstrate that PXRDs are acceptable ways of characterizing crystalline forms, including crystalline forms of carvedilol. See, e.g., Wall, Pharmaceutical Manufacturing, February, 1986, Vol. 3, No. 2, pp. 33-42 (Exhibit A), at p. 35, right column:

> The most definitive analysis of crystalline-state structure is given by x-ray diffraction studies. Diffraction patterns may be obtained from either a single

> crystal or a powdered specimen. In single-crystal studies, the x-ray reflection angles off of the rotating crystal are compiled, and interatomic distances, ring planes, and dihedral angles are determined based on these angles. More commonly in polymorphic studies, however, x-ray diffractograms of powdered samples are compared for qualitative differences. [emphasis added]

See also Rouhi, at p. 32:

> Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. Although identical in chemical composition, polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. [emphasis added]

The present application describes and claims a crystalline form of carvedilol that are referred to therein as "Form VI." Form VI is described in the present application as being a crystalline form of carvedilol that are characterized by, inter alia, certain 2θ peaks in its PXRD pattern. See, for example, page 4, lines 9-13, of the present application.

From the descriptions of 2θ peaks in the present application referred to in the preceding paragraph, one of ordinary skill in the art would understand that, at least as early as the filing date of the present application, the inventors of the present application possessed and had invented a crystalline form of carvedilol referred to therein as Form VI that is characterized by an X-ray diffraction pattern with the following characteristic 2θ peaks: 6.5, 7.3, 16.0, and 30.5±0.2 degrees 2θ. One of ordinary skill in the art would also understand that Form VI can be further characterized by 2θ peaks at 5.8, 10.7, 11.1, 11.5, 13.1, 13.7, 16.8, 17.7, 18.5, and 23.0±0.2 degrees 2θ.

From the descriptions in the present application referred to in the preceding paragraphs, one of ordinary skill in the art would understand that Form VI is a crystalline form of carvedilol and that the 2θ peaks of Form VI disclosed in distinguish Form VI from other crystalline forms of carvedilol.

The Office Action provided no evidence that one of ordinary skill in the art would doubt that the Applicants possessed or had invented the claimed invention. Assuming the Office Action is correct and that an x-ray diffraction pattern is like a fingerprint, this would support the Applicant's position. The recited PXRD peaks, like distinguishing whorls and other characteristics of fingerprints that serve to distinguish one fingerprint from another, distinguish the claimed crystalline Form VI from other crystalline forms and thus convey to one of ordinary skill in the art that the Applicants possessed and invented the claimed crystalline form.

In another aspect of this rejection, the Office Action, at page 15, finds a lack of written description because the claims do not recite all the PXRD peaks of the claimed crystalline form and because the specification does not explain why all the PXRD peaks are not recited.

> The peaks present in the claims 1-3, 5-10 and 17-21 do not include all peaks of the x-ray diffraction pattern. ... Applicant has not provided why the entire "fingerprint" is not being claimed ... The claims to only certain peaks do not find written description in the specification as the claims do not include the enter [sic, entire?] "fingerprint" and the specification fails to provide any description as to why the data claimed is characteristic of Form VI and why the entire "fingerprint" is not required.

There is no requirement that a claim must recite every feature of an invention to satisfy the written description requirement. All that is required is that the specification clearly convey to one of ordinary skill in the art that the Applicants possessed or had invented what is recited in the claims. There is no need for the claims to recite every possible of feature of the invention for the specification to accomplish this.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claim 10 was rejected as being indefinite.

The reason for this rejection appears to be that claim 10 recited no data. Claim 10 has now been amended to recite Differential Thermal Gravimetry data. In view of this, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §§102(a), (b), and (e)

Claims 10 and 17 were rejected as anticipated under 35 U.S.C. §102(b) by Chen et al., 1998, Chinese J. Struct. Chem. 17:325-328 (Chen).

Claims 10 and 17-21 were rejected as anticipated under 35 U.S.C. §102(b) by U.S. Patent No. 4,503,067.

Claims 10 and 17-19 were rejected as anticipated under 35 U.S.C. §102(b) by EP 0918055.

Claims 10 and 17-21 were rejected as anticipated under 35 U.S.C. §102(b) by EP 0893440.

Claims 10 and 17-21 were rejected as anticipated under 35 U.S.C. §102(b) by WO 99/05105.

Claims 10 and 17-21 were rejected as anticipated under 35 U.S.C. §§102(a) and (e) by WO 02/00216.

Claims 10 and 17-19 were rejected as anticipated under 35 U.S.C. §102(e) by US 2004/152756.

With respect to claim 10, these rejections appear to be based on the position that claim 10 did not recite data characterizing Form VI (see the Office Action, page 4: "claim 10 has no limiting element to define a difference from any carvedilol").

Claim 10 has now been amended to recite Differential Thermal Gravimetry data. Accordingly, it is respectfully requested that these rejections be withdrawn with respect to claim 10.

Claim 17 has been canceled.

With respect to pharmaceutical composition and dosage form claims 18-21, the Office Action, at page 4, stated: "[T]he rejection is maintained for the pharmaceutical composition claims, which have not been demonstrated to be in Form VI in the instant specification.

This reasoning appears to be the same as that discussed above in connection with the enablement rejection of the pharmaceutical composition and dosage form claims. The Applicants submit that this reasoning is in error for the reasons discussed above in connection with the enablement rejection. Accordingly, it is respectfully requested that these rejections be withdrawn with respect to claims 18-21.

<u>The rejections under 35 U.S.C. §103</u>

Claims 1-10 and 17 were rejected as being obvious over Chen et al., 1998, Chinese J. Struct. Chem. 17:325-328 (Chen) in view of Grell et al., 1998, J. Med. Chem. 41:5219-5246 (Grell) and Byrn et al., "Solid State Chemistry of Drugs," 1999, pages 62-63 (Byrn).

Claims 1-10 and 17-21 were rejected as being obvious over U.S. Patent No. 4,503,067 in view of Grell or Byrn.

Claims 1-10 and 17-19 were rejected as being obvious over EP 0918055 in view of Grell or Byrn.

Claims 1-10 and 17-21 were rejected as being obvious over EP 0893440 in view of Grell or Byrn.

Claims 1-10 and 17-21 were rejected as being obvious over WO 99/05105 in view of Grell or Byrn.

Claims 1-10 and 17-21 were rejected as being obvious over WO 02/00216 in view of Grell or Byrn.

Claims 1-10 and 17-21[2] were rejected as being obvious over U.S. Patent Publication No. 2004/152756 in view of Grell or Byrn.

As discussed below, all these obviousness rejections are similar and suffer from the same defects. In each rejection, the first cited reference is relied upon for the disclosure of a

[2] The Office Action states "claim 1-10 and 121." The Applicants presume the "121" is a typographical error since there is no claim 121.

crystalline form of carvedilol that is different from the claimed Form VI and the use of the secondary references and supporting arguments is similar.

The difference between the crystalline forms of the primary references of these rejections and the claimed Form VI is that the crystalline forms of the primary references and Form VI are different crystalline forms with different physical characteristics such as X-ray diffraction patterns (see, e.g., the Office Action, page 19: "The difference between the prior art and the instant claims is that the X-ray diffraction pattern [sic, of] the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.") The Office Action states that one would be motivated to make Form VI in order to secure a pure product. See the Office Action, page 20: "One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product." Grell was cited for the proposition that "The employment of different solvents in the crystallization process are [sic] art recognized conventional variation for obtaining different forms ..." Byrn was said to disclose that an X-ray diffraction pattern may include artifacts. *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) was cited as supporting this rejection.

The Applicants traverse this rejection. It is respectfully submitted that this obviousness rejection relies on hindsight based on the Applicants' disclosure that the claimed crystalline Form VI exists. Before the Applicants' invention, Form VI was an unknown substance. Moreover, there were no known ways of making Form VI. That some other crystalline form such as those disclosed in the primary references might have existed does not make obvious the <u>particular</u> claimed crystalline Form VI since there could have been no motivation to produce Form VI when Form VI was not known to exist. Also, there could have been no reasonable expectation of successfully producing Form VI when there was no

known way of making Form VI. Furthermore, the most pertinent case law supports a conclusion that the presently claimed Form VI is non-obvious.

This rejection is based on the premise that motivation to make the present invention could be found in the knowledge of the existence of prior art crystalline forms and the possibility that additional crystalline forms of carvedilol might exist. Such "motivation," even if it existed, is not specific enough to provide the motivation necessary to sustain an obviousness rejection of the present claims. Such motivation is not specific to Form VI. It represents a general incentive to look for additional crystalline forms, once it is known that crystalline forms of a compound exist. But this is not sufficient motivation to sustain an obviousness rejection. "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559, 34 U.S.P.Q. 2d 1210, 1216 (Fed. Cir. 1995).

The present claims are directed to specific subject matter – a particular crystalline form of carvedilol. At most, the existence of other crystalline forms of carvedilol in the prior art could have provided a general suggestion to explore the possibility that there may be additional carvedilol crystalline forms in addition to those already known. As explained below, the Court of Appeals for the Federal Circuit has held that such general motivation to explore a new area is insufficient to sustain an obviousness rejection. Moreover, decisions of various tribunals in connection with the obviousness of crystalline forms have repeatedly found that such general motivation is inadequate.

In order to arrive at the presently claimed crystalline form, based merely on the general motivation provided by the existence of other crystalline forms, one skilled in the art would have had to vary a large number of parameters in an attempt to find the right

parameters for producing the claimed crystalline form. Among such parameters would be: solvent or solvent systems, temperature, time of reaction, and carvedilol starting material (i.e., type of crystalline form or amorphous form). All of these parameters would have to be varied independently, without any specific guidance from the prior art. It can readily be seen that the number of permutations of these parameters would be enormous, with no guidance to narrow down the possibilities.

In view of the lack of specific guidance in the prior art, and the large number of parameters to be varied, the argument provided in the Office Action at most demonstrates that it might have been "obvious to try" to make the claimed invention. The argument in the Office Actions thus falls into the type of obvious-to-try error cautioned against by the Federal Circuit in *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988):

> The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Furthermore, given the total lack of guidance in the prior art as to the specific reaction parameters that would have led to the claimed crystalline form, the argument provided in the Office Action demonstrates at most that those skilled in the art would have been motivated to explore a promising field of experimentation. Thus, the argument in the Office Action also falls into the second type of error cautioned against by the Federal Circuit in *O'Farrell*:

> In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

853 F.2d at 903, 7 USPQ2d at 1681.

See also *Ex parte Obukowicz*, 27 USPQ 2d 1063, 1065 (Bd. Pat. App. & Int. 1992):

> At best, the [cited reference] is but an invitation to scientists to explore a new technology that seems a promising field of experimentation. The [cited reference] is of the type that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it. Such a suggestion may make an approach "obvious to try" but it does not make the invention obvious.

Case law in which the obviousness of crystalline forms was at issue supports the Applicants' position. In *In re Certain Crystalline Cefadroxil Monohydrate*, 15 USPQ2d 1263 (U.S. Intern. Trade Comm. 1990), the U.S. International Trade Commission (ITC) reversed a finding of one of its administrative law judges (ALJs) that a Bristol-Myers patent claiming a particular crystalline form of cefadroxil was obvious over two prior art patents that disclosed processes for producing various forms of cefadroxil.

Using reasoning similar to that of the current Office Action, the ALJ based her conclusion of obviousness on a determination that there was a general motivation to find other crystalline forms of cefadroxil and that the claimed crystalline form could have been obtained by methods that were obvious to those of ordinary skill in the art. The ITC summarized the ALJ's reasoning as follows:

> [T]he ID[3] concluded that if these prior art methods were modified in a certain manner, using changes obvious to those with ordinary skill in the art, the Bouzard monohydrate[4] would be produced.
>
> In effect, the ALJ concluded that because there was motivation to make a commercially usable form of cefadroxil, and obvious changes to the processes described in the prior art would result in production of the Bouzard

[3] "ID" refers to "initial determination," the name given to the ALJ's report.

[4] The Bouzard monohydrate was the crystalline form of cefadroxil claimed in the Bristol-Myers patent at issue.

monohydrate, which has been commercially successful, the Bouzard monohydrate was obvious under 35 U.S.C. §103. We do not believe that either the ID's inquiries or its conclusions comport with controlling law. The ID's method of analysis is, in fact, identical to that found in the TEO ID, which the Federal Circuit[5] rejected as:

> irrelevant to whether the Bouzard discovery would have been obvious in terms of §103. The question before the Commission was not whether the Bouzard crystal form could have been duplicated with experimentation or with even minor chemical process changes; the question was whether this new crystal form, as a composition of matter, would have been obvious from the teachings of the prior art.
>
> • • •
>
> It is insufficient that the prior art shows methods that some (but not all) chemists were able to modify, to produce the Bouzard crystalline form. There must be a suggestion in the prior art that the Bouzard crystal structure would or should be made, whether by manipulation of the Garbrecht or Crast II[6] processes, or by any other process. In factual and legal point is In re Cofer, 354 F.2d 664, 668, 148 USPQ 268, 271 (CCPA 1966), wherein the court held that a new crystalline form of a compound would not have been obvious absent evidence that "the prior art suggests the particular structure or form of the compound or composition as well as suitable methods for obtaining that structure or form."

15 USPQ2d at 1268 [footnotes omitted, emphasis added]

The ITC went on to find the Bristol-Myers patent non-obvious, stressing that the motivation in the prior art was too general, i.e., not directed to the particular claimed crystalline form and that the particular claimed crystalline form was unpredictable:

> The ID merely determined that motivation existed to produce an improved form of cefadroxil - not the particular structure represented by the Bouzard monohydrate. ... The ID further found that:

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[5] In prior proceedings concerning this dispute, the ITC had denied Bristol-Myers temporary relief (a "TEO") because the ITC concluded that the Bristol-Myers patent was likely to be found invalid for obviousness over the two prior art patents. The Federal Circuit reversed this decision on temporary relief, finding that the Bristol-Myers patent would likely be found non-obvious over the two patents. This Federal Circuit decision was reported at Bristol-Myers Co. v. U.S. International Trade Commission, 15 USPQ2d 1258 (Fed. Cir. 1989) as a non-precedential decision. Thus, this Federal Circuit decision is not binding precedent, although the Applicants believe the reasoning therein is persuasive and would likely be followed again, were the Federal Circuit faced with similar facts.

[6] Garbrecht and Crast II were the two prior art patents.

> the form of cefadroxil could not be predicted accurately until the experiment was made. Dr. Garbrecht expected that the cefadroxil DMF solvate produced by his '282 patent process would be crystalline, and that the final product of the aqueous crystallization procedure would be a solid, but he had no expectations about the nature of its crystallinity or hydration. (Tr. 342-44.) Dr. Baldwin [a Bristol expert witness] agreed with Dr. Garbrecht, and testified that no chemist could predict the form of hydration that a cefadroxil crystal could take. (Tr. 228.)
>
> Respondents have not disputed or contested this finding. To the contrary, one of their own expert witnesses also testified that he would not have been able to predict in advance the form of the Bouzard monohydrate.
>
> Consequently, the record indicates that the prior art did not and could not have suggested the particular structure and form of the Bouzard monohydrate. Respondents argue that the "predictability" of the Bouzard monohydrate has no relevance to a determination on obviousness, and instead direct our attention to the evidence that they submitted and the ID discussed concerning the obviousness of the modifications to the Crast and Garbrecht patents needed to produce the Bouzard monohydrate. The Federal Circuit, however, has ruled that "predictability" does matter, and that respondents' reliance on the obviousness of changes to prior art processes is in vain ...
>
> 15 USPQ2d at 1269-1270 [footnotes omitted]

The facts in the present application are similar to those of *In re Certain Crystalline Cefadroxil Monohydrate.* The presently claimed crystalline form was unknown and its structure was thus unpredictable before the Applicants' invention. The motivation cited by the Office Action in the present application, like the motivation in *In re Certain Crystalline Cefadroxil Monohydrate,* is merely general, not directed to the particular claimed crystalline form. Since the Office Action provided no evidence that the prior art contained disclosures of processes that could be used to make Form VI, the Office Action must be relying on the obviousness of changes to prior art processes. The losing party in *In re Certain Crystalline Cefadroxil Monohydrate* similarly relied on changes to prior art processes. These similarities between the present rejection and *In re Certain Crystalline Cefadroxil Monohydrate* should

lead to the same conclusion as in *In re Certain Crystalline Cefadroxil Monohydrate* – the presently claimed crystalline Form VI is non-obvious.

Although cited in the Office Action, *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) support the Applicants' position. In *Cofer*, the Board of Appeals (quoting *Hartop*) had sustained a rejection for obviousness of a new crystal form of a compound, stating:

> [M]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable ...
>
> 354 F.2d at 667, 148 USPQ at 271.

The Court of Customs and Patent Appeals ruled that the broad proposition embodied in the Board's statement was not sound. The Court stated:

> The cited cases fail to support the broad proposition that:
> . . . merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable.
>
> 354 F.2d at 667, 148 USPQ at 271.

The Court went on to state that the factors to be given weight in determining whether the claimed crystalline form was obvious were whether the <u>particular</u> claimed crystalline structure was suggested by the prior art and whether the prior art provided <u>methods of obtaining</u> that <u>particular</u> structure.

> We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the <u>particular</u> structure or form

> of the compound or composition as well as suitable methods of obtaining that structure or form. [emphasis added]
>
> 354 F.2d at 668, 148 USPQ at 272.

Since neither the particular claimed structure, nor methods of obtaining that structure, were disclosed in the art, the Court reversed the rejection for obviousness.

Applying the reasoning of *Cofer* to the present claims leads to a conclusion of non-obviousness since the prior art suggests neither the particular structure of the presently claimed crystalline Form VI nor methods of obtaining the claimed crystalline Form VI.

Other case law supports a finding of non-obviousness for the present claims. In *In re Irani*, 427 F.2d 806, 166 USPQ 24 (CCPA 1970), the Court of Customs and Patent Appeals again reversed the Board of Patent Appeals after the Board held obvious claims to a crystalline form of a compound based on a disclosure of a non-crystalline form of the same compound. The Court found that the prior art did not suggest that the particular claimed crystalline compound existed or provide a method for making it.

> Upon due consideration of all these reference disclosures concerning the physical forms in which various known aminophosphonic acids exist, we think the most definite conclusion that can be reached is that some of these acids can be obtained in crystalline form and some cannot, and that of the former group some can be obtained with ease by conventional procedures and some only with great difficulty by specially devised techniques. This being the case, we cannot conclude that it would have been obvious that crystalline, anhydrous ATMP could exist.
>
> As stated above, even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline anhydrous ATMP could be produced, we are not convinced by this record that it would also have been obvious *how* this could be achieved. We note that neither the examiner nor the board has contended that a suitable process would have been obvious. [italics in original]
>
> 427 F.2d at 809, 166 USPQ at 27.

The present situation is similar to that in *Cofer* and *Irani*. The prior art fails to suggest the existence of the particular claimed crystalline form and the prior art fails to suggest methods by which that particular crystalline form can be obtained. Given the holdings in *Cofer* and *Irani*, it is clear that the present claims, like those in *Cofer* and *Irani*, are not obvious.

The lack of disclosure of a method of making the claimed crystalline Form VI in the prior art leads to a conclusion of non-obviousness for the present claims not only under *Cofer* and *Irani* but also under *In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979). In *Grose*, the court made it clear that a conclusion of obviousness of one compound based upon its structural similarity to another compound depends upon the assumption that the method disclosed for producing the prior art compound can be used to produce the new compound.

> One of the assumptions underlying a prima facie obviousness rejection based upon a structural relationship between compounds, such as adjacent homologs, is that a method disclosed for producing one would provide those skilled in the art with a method for producing the other.

592 F.2d at 1168, 201 USPQ at 63.

> Failure of the prior art to disclose or render obvious a method for making any composition of matter ... precludes a conclusion that the composition would have been obvious.

592 F.2d at 1168, 201 USPQ at 64.

There is no evidence of record that shows that the presently claimed crystalline Form VI can be produced by the methods disclosed in the prior art. Given that the production of particular crystalline forms is highly sensitive to the precise reaction conditions used, it is highly likely that the prior art methods could not produce the presently claimed crystalline form. The prior art is devoid of any suggestion as to the particular modifications of prior art

processes that would lead to the production of the particular claimed crystalline Form VI. Accordingly, the presently claimed crystalline Form VI is non-obvious under *Grose*.

Another case holding that the disclosure of one crystalline form of a pharmaceutical compound does not make obvious other, different forms is *Ex parte Gala*, 2002 WL 851814 ((Board of Patent Appeals & Interferences, date unavailable).[7] In *Ex parte Gala*, the Board reversed a rejection for obviousness of claims directed to a particular crystalline form of a pharmaceutical compound, Form 2 of loratadine. The cited art included a patent (Villani) that disclosed a different crystalline form of loratadine, Form I.

> Villani discloses polymorph form 1 of loratadine, but does not disclose or suggest that loratadine may assume distinct, crystalline polymorphic forms having different physical properties. Nor does Villani teach a person having ordinary skill in the art how to make polymorph form 2 of loratadine.
>
> *Ex parte Gala*, page 2.

The Examiner in *Gala* had relied on *Hartop*, stating: "[M]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable." (*Ex parte Gala*, page 3). The Board summarized the Examiner's reasoning as follows:

> According to the examiner, polymorph form 2 loratadine is merely another form of an old product (polymorph form 1 loratadine) and both forms possess the same utility. Accordingly, the examiner concludes that applicants' claims, reciting polymorph form 2 loratadine, are unpatentable.
>
> *Ex parte Gala*, page 3.

The Board rejected this reasoning and reversed the rejection, stating that *Cofer* "substantially discredited" this reasoning.

---

[7] A copy of this decision was provided with the previous Amendment as Exhibit A.

The current rejection is inconsistent with well-established principles relating to the issue of obviousness of chemical compounds. It is well settled that the properties of a claimed chemical compound must be taken into account when conducting an obviousness inquiry. See, e.g., *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963): "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." The *Grose* court reiterated this principle and stated that differences in X-ray diffraction patterns between a claimed compound and prior art compounds were among the types of differences in properties that support a conclusion of non-obviousness for claimed compounds.

> Determining whether a chemical composition is prima facie obvious from another may rest on whether differences in structure and properties of the compositions can be accounted for by obvious modifications in the synthesis process or by obvious modifications of one composition to yield the other. If the differences in X-ray diffraction data between the zeolites here involved had indicated an actual difference in crystal structure, the present record would belie a conclusion that such differences resulted from obvious modifications of any prior art synthesis process or from obvious modifications of Milton's zeolite R to yield the claimed zeolite.

592 F.2d at 1168, 201 USPQ at 63.

The X-ray diffraction pattern of the presently claimed crystalline Form VI differs from the X-ray diffraction patterns disclosed in the prior art. These differences represent real, significant differences in structure, and thus properties, between Form VI and prior art forms. "Because of differences in the dimensions, shape, symmetry, capacity (number of molecules), and void volumes of their unit cells, the different polymorphs of a given substance have different physical properties arising from differences in molecular packing." David J. W. Grant, *Theory and Origin of Polymorphism,* in Drugs of the Pharmaceutical Sciences, vol. 95, Polymorphism in Pharmaceutical Solids, Chapter 1, sentence connecting pages 5 to 8

(Harry G. Brittain ed., 1999).[8] Physical properties that may differ among various polymorphs include: packing properties, thermodynamic properties, spectroscopic properties, kinetic properties, surface properties, and mechanical properties. *Id.* at 7. Because different crystalline forms exhibit different structure and different properties, the disclosure of one crystalline form does not render obvious another crystalline form. The different structures and different properties of crystalline forms make this art unpredictable. There is a large amount of uncertainty involved in arriving at any particular crystalline form, or even knowing that such a form exists. The process of making new crystalline forms is essentially a process of trial and error. See, e.g., Rouhi, at p. 32: "But no method yet exists to predict the polymorphs of a solid compound with significant certainty. The search for polymorphs is largely an empirical exercise." The Patent Office has recognized this unpredictability by routinely granting patents for novel crystalline forms over both the free form and other known crystalline forms.

In view of the above, it is respectfully requested that these rejections be withdrawn.

The time for responding to the Office Action was set for August 25, 2007. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this paper. Charge any fees associated with the Petition for the Extension of Time to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's

[8] A copy of Grant was enclosed with the previous Amendment as Exhibit B.

Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

Date: NOV. 26, 2007

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APPLIED TECHNOLOGY FOR PROCESS ENGINEERING, PRODUCTION, QA, AND R&D

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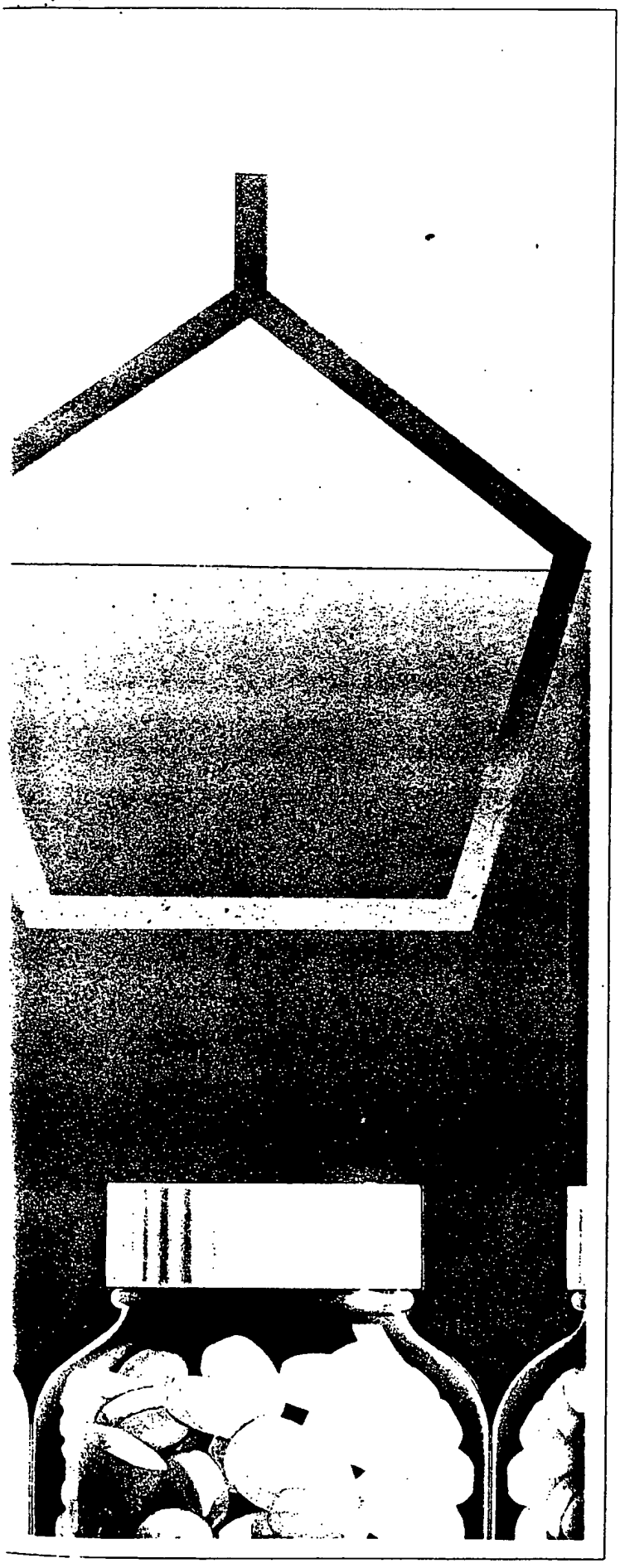


Pharmaceutical Applications of Drug Crystal Studies

G. Michael Wall

Many drugs exist in one or more crystalline forms, either alone or in combination with other drugs, excipients, or solvent molecules. As crystalline configurations vary, lattice energies will also vary, and the different crystal forms may act as if they were different compounds, manifesting differences in melting point, solubility, dissolution rate, density, hardness, and/or chemical stability. Such variations can have serious effects when compounds are used as pharmaceutical agents. For example, a polymorphic drug may change its crystal structure upon compression or grinding during the tabletting process or during scale-up procedures using differing solvent ratios, and the resulting variation could drastically affect the pharmaceutical product's solubility or dissolution rate and, hence, its bioavailability.

The early literature covering pharmaceutically significant aspects of crystal theory contains several excellent reviews,[1-3] including a report on polymorphism in pharmaceutical formulations[2] and a classic review of crystal habits containing specific information on solvates and clathrates.[3] The object of this paper is to provide an overview of the subject and an update on the many recent studies of polymorphism and crystal adducts of commercially available organic drugs.

TERMINOLOGY AND NOMENCLATURE

A pure drug that exhibits more than one crystalline form is known as *polymorphic*, the term *polymorphs* referring to compounds having exactly the same chemical composition. Upon crystallization, however, a crystal may incorporate solvent molecules into its lattice structure, resulting in a crystal adduct called a *solvate*. If the solvent incorporated is water, such a crystal is called a *hydrate*. Obviously, solvates can also exhibit polymorphism; however, solvated and nonsolvated polymorphs of the same compound should be referred to as *pseudopolymorphs* because the crystals of the two types of polymorphs are in fact of different chemical composition. For example, chlordiazepoxide hydrochloride has been shown to exhibit two polymorphic forms and one pseudopolymorphic (monohydrate) form.[4] Cases of polymorphs and solvates constitute the bulk of reports on variations in drug crystals.

Different crystal lattice configurations are associated with different energies, and, for each compound, one configuration will exhibit energy characteristics that render it the most stable. The less-stable (higher-energy) polymorphs are known as *metastable*. In the literature, metastable polymorphs are sometimes also referred to as "unstable." However, the heats of transition of metastable polymorphs can be quite high, resulting in an adequately "stable" form for most practical purposes.

In dealing with stable and metastable polymorphs, two other terms are sometimes encountered: *monotropic* and *enantiotropic*. Expert sources should be consulted for strict definitions.[2,5] For simplicity, however, consider the hypothetical case of two polymorphic pairs, each consisting of a metastable and a stable polymorph. For pair one, heating will cause both polymorphs to pass directly into the liquid phase, but for pair two, upon heating the metastable polymorph will first be transformed into the configuration of the stable polymorph, which will in turn liquefy. The first pair of polymorphs have a monotropic relationship, whereas the second are referred to as enantiotropic. (These hypothetical cases represent ideal situations: in reality, the distinction is often difficult to observe in the laboratory.)

As far as crystal nomenclature is concerned, there is no universally accepted numbering system for polymorphs. The designation of forms 1, 2; I, II; A, B; or α and β does not imply any information on stability or metastability. When a particular solid state is obtained during drug development, it may not be possible to determine whether that form has the lowest possible energy. Therefore, the form designations of a polymorph may indicate the chronological order of discovery, or, if several were discovered simultaneously, may indicate a logical progression in the ascending order of their melting points.

DETECTION METHODS

Several analytical methods are commonly used to study polymorphs, including thermoanalysis, infrared (IR) spectroscopy, and x-ray diffraction. A brief description of each and some applications follow.

Thermoanalysis. The thermoanalytical methods most often used for pharmaceuticals are differential scanning calorimetry (DSC) and differential thermal analysis (DTA). These methods both provide thermograms that illustrate endothermic (heat absorption) or exothermic (heat loss) transitions in solids. The presence of a multiplicity of peaks in a thermogram usually indicates polymorphism.

In DSC, a sample and a reference standard are placed in separate containers, which are gradually heated at a constant rate. As the sample melts, there is a temperature lag behind that of the standard. In order to compensate for this temperature difference, the instrument provides heat input to the sample and records this input, which may be quantitated. Melting usually causes an

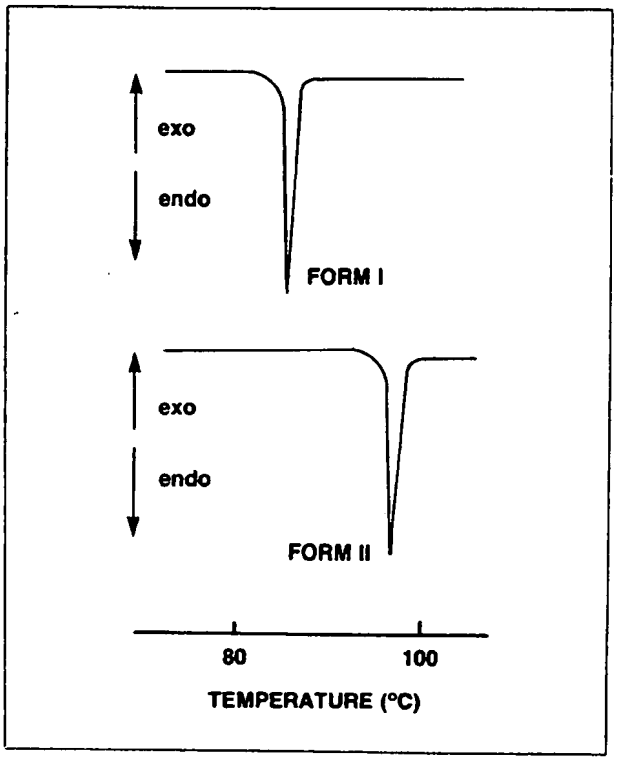
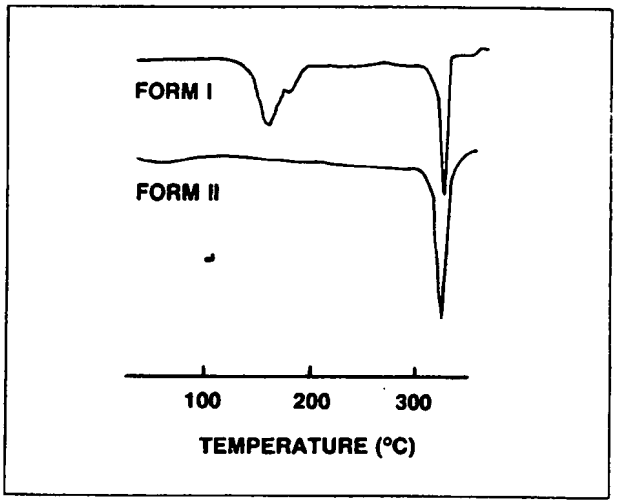


Figure 1: Differential calorimetric scan showing the presence of disopyramide polymorphic forms I and II.

Figure 2: Differential thermograms of commercial (form I) and heat-treated (form II) samples of mercaptopurine.



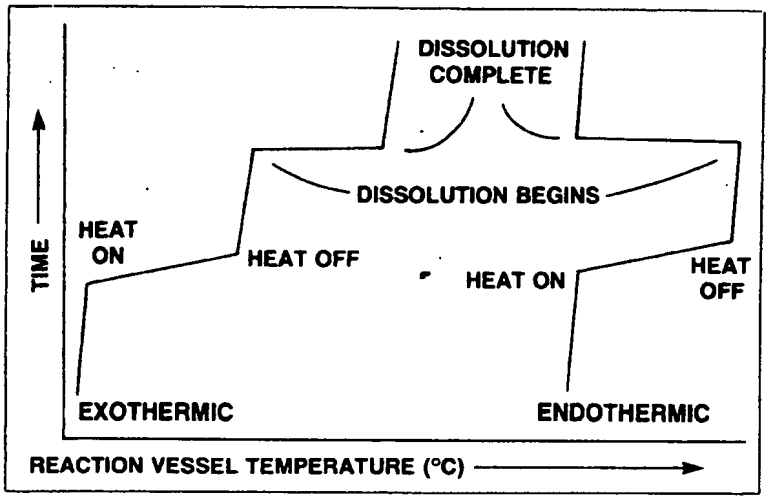
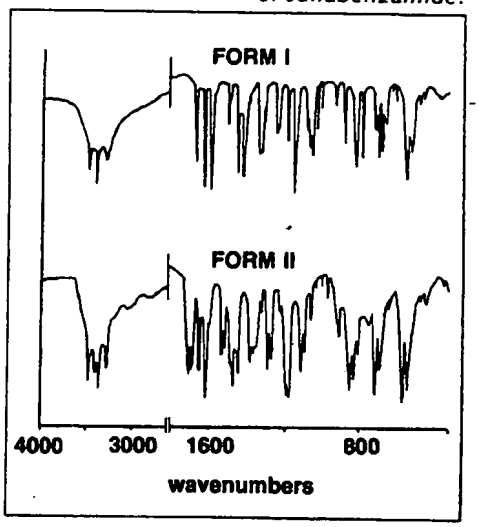


Figure 3: Solution calorimetric thermograms for typical exothermic and endothermic reactions.

Figure 4: Infrared spectra of polymorphic forms I and II of sulfabenzamide.



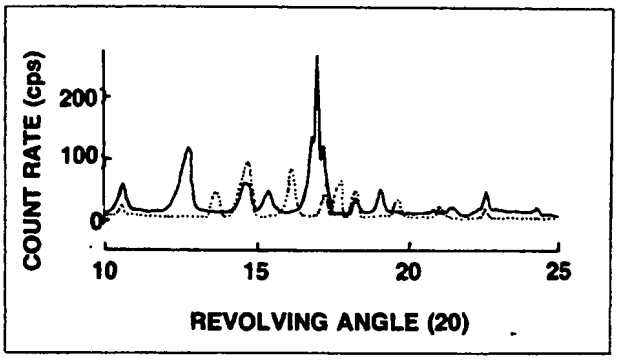


Figure 5: X-ray diffraction patterns for pulverized samples of α and β forms of progesterone. Solid line shows α; dotted line shows β.

endothermic peak in a thermogram. Figure 1 illustrates how DSC was used to identify polymorphic forms I and II of disopyramide; the thermograms' peaks reveal endothermic absorptions at their respective melting points (86° and 97°C).[6]

Differential thermal analysis, also employed in drug crystal studies, is more qualitative than is DSC. In DTA, a sample and reference standard are heated by a common source, and thermocouples placed in contact with them monitor temperature differences, which are plotted against time. DTA has been used to show that commercially available mercaptopurine exists in polymorphic form I—indicated by the two endothermic transitions illustrated in Figure 2—and that incubation of the drug results in a new form (II), which displays only one endothermic transition, also shown in the figure.[7]

In addition to DSC and DTA, solution calorimetry has also been useful in studying polymorphs.[8-10] Since different crystalline or amorphous configurations have different lattice energies, their heats of solution in any given solvent also differ. These heats of solution are measured with a calorimeter connected to a chart recorder. As the drug dissolves in the calorimeter solvent, time-versus-temperature plots are recorded (see Figure 3). This method has been employed to show morphological differences in crystals of β-lactam antibiotics,[8] bendroflumethiazide,[9] indomethacin,[10] and sulfathiazole.[9]

Infrared Spectroscopy. IR spectroscopic evaluation of crystalline compounds is a routine part of most polymorphic studies. The spectra are produced from the solid form as an oil suspension or potassium bromide pellet since solution spectra of polymorphs would look identical. Frequencies of IR absorption correlate closely with vibrations from various parts of the molecule. This technique was useful in identifying tautomeric polymorphs of sulfabenzamide,[11] the spectra of which are shown in Figure 4.

X-ray Diffraction. The most definitive analysis of crystalline-state structure is given by x-ray diffraction studies. Diffraction patterns may be obtained from either a single crystal or a powdered specimen. In single-crystal studies, the x-ray reflection angles off of the rotating crystal are compiled, and interatomic distances, ring planes, and dihedral angles are determined based on these angles. More commonly in polymorphic studies, however, x-ray diffractograms of powdered samples are compared for qualitative differences. For example, this technique was useful in establishing the presence of α and β forms of progesterone in powdered samples (see Figure 5).[12]

Text continued on page 37

RECENT POLYMORPHIC STUDIES

Drug	Number of Polymorphic Forms[a]	References
Acetamide	2	56
Acetaminophen	2	56
Acetohexamide	4(1), 4	57
	4	57
	3	24, 56
	2	58, 59
	NA[b]	60
Acetylsalicylic acid	3	40
	1	61
Amobarbital	NA	62
Amobarbital sodium	1, 1	63
Ampicillin	2, 1	13
Azaperone	2	41, 64
Benactyzine hydrochloride	NA	65
Bendroflumethiazide	2	9
Benperidol	3, 2	66
Betamethazone acetate	NA	67
Betamethazone dipropionate	NA	67
Butabarbital	2	68
Butacaine sulfate	2	16
Caffeine	2	39, 69
Carbromal	1(1)	30
	3	70
Cefamandole naftate	1(2), 1	8
Cefamandole sodium	(2), 2	8
Cefazolin sodium	1(2), 2	8
	1(1)	71
Cephalexin	1, 8	22
	1, 4	72
Cephaloglycin	1, 10	22
Cephalothin sodium	1(1)	8
Chloramphenicol palmitate	4	56, 73
	3	21
	2	74, 75, 76
	1	77
Chlordiazepoxide hydrochloride	2, 1	4
Chloroquine diphosphate	2	78
Chlorothiazide	1(1)	18, 79
Chlorpropamide	5, 1	80
	5	25, 56
	3	39
	NA	61
Cimetidine	3, 1	20
Clotrimazole	2	41
Codeine	3	81
Cyclophosphamide	1, 1	82
Dapsone	NA	83
Difenoxin hydrochloride	2	84
Digitoxin	NA	85
Digoxin	3(1)	86
	3	87
	2 or 3	85
	1(1)	17
Dimethoxanate hydrochloride	NA	88
Diphenadione	NA	88
Diphenidol	NA	65
Dipyridamol	2	39
	NA	65
Disopyramide	2	6, 56
Droperidol	3, 1	66
Erythromycin	1(1), 1	89
Erythromycin estolate	NA	90
Estradiol	1(1)	17
	NA	91
Ethambutol dihydrochloride	NA	83
Ethinyl estradiol	3, 3	92
Ethyl biscoumacetate	2	56
	NA	93
Fluanisone	3	64
Flucloxacillin	1, 2	94
Flufenamic acid	5	56, 95, 96
Glymidine sodium	2	97
Griseofulvin	1, 3	14
	1, 2	13
Homatropine hydrochloride	2	98
Hydrocortisone	1(1)	99
	1	100
Hydroflumethiazide	1(1)	31
Indomethacin	2	10, 35, 101, 102, 103
Maprotiline hydrochloride	3	39
	NA	88
Mebendazole	5	39
Medrogesterone	NA	104
Mefenamic acid	2	56
	NA	95
Menadione	3	56
Meprobamate	3	51, 105
	2	56, 106
Mercaptopurine	2	7
Metahexamide	4, 1	107
	4	56
Methisazone	3	42
Methylprednisolone	2	56
Methyltestosterone	2	108
Metronidazole benzoate	2, 1	109
Nabilone[c]	4(1)	55
Nafcillin	1(1)	71
Nicergoline	2	110
Nicotinamide	3	56
Nifedipine	2	111
Nystatin	2	37
Oxyclozanide	3	56
Penicillamine	2	112
Penicillin G	1(1)	8
Pentobarbital	3	39
	2	113
Phenobarbital	4	56
	2, 1	36
	2(1)	31
	1(1)	30, 32, 43
	NA	62

Drug	Number of Polymorphic Forms[a]	References
Phenobarbital sodium	2	114
Phensuximide	NA	104
Phenylbutazone	5	26
	4	33, 45
	3	27, 28, 56, 115
	2, 2	116
	2	44
Phenylpropylmethylamine hydrochloride	2	56
Phenytoin	2	117
Prednisolone	1, 1	54
Prednisone	1(1)	99
	NA	68
Progesterone	2	12, 56, 118, 119
Propantheline bromide	2	120
Propyphenazone	2	121
Prothioamide	2	56
	NA	104
Rifampicin	NA	122
Spironolactone	4	123
	1(1)	17
Succinylsulfathiazole	2(1), 4	124
Sulfabenzamide	2	11, 39, 125
Sulfaethidole	2	56
Sulfaguanidine	2	56
	NA	50
Sulfameter	5	56
	4, 4	126
	2	38, 127
Sulfamethoxazole	5	128
	3	53
	2(1)	34
	1(1)	52
Sulfamethoxypyridazine	3	56
Sulfanilamide	4	129
	3	47, 56
	NA	48, 130
Sulfapyridine	5	131
	4	56
	3	19
	2(1), 3	132
Sulfathiazole	3(1)	133
	3	56
	2	9, 29, 40, 49
	NA	134
Sulfazamet	2	56
Testosterone	2	108
Tetracaine hydrochloride	3	56
Theophylline	2	56
	NA	135
Tolbutamide	4	23, 56, 136
	3(1)	137
	2	15
	NA	61
Triamcinolone diacetate	2(1)	138
Trimethoprim	3(3)	139, 140
	2	141

[a]Crystal (amorphous), solvate forms.
[b]Evidence of polymorphism noted. Specific number of forms may or may not be available in literature.
[c]Not yet commercially available.

Other Techniques. Traditional methods such as hot-stage microscopy also are still useful in polymorphic studies. Hot-stage microscopy is actually a thermoanalytical technique in which solid-solid transitions are visually observed during melting, cooling, and remelting. Two other methods have been documented to a lesser extent in polymorphic studies: Laser Raman spectroscopy has been employed in the identification of the solvates of griseofulvin,[13,14] and the polymorphs of ampicillin,[13] sulfabenzamide,[11] and tolbutamide;[15] and electron microscopy has been incorporated into polymorphic studies on butacaine sulfate,[16] digoxin,[17] and thiazide diuretics.[18]

Interpretation of polymorphic data is gradually improving from empirical observations to detailed analyses of chemical bonding mechanisms within the crystal. For example, the specific tautomers involved in the conformational polymorphism of sulfabenzamide[11] and sulfapyridine[19] have been determined. As Figure 6 shows, these compounds have the potential to exist as either amides or imides within the crystal. Sulfabenzamide polymorphs exhibit both an amido form (form I) and an amido-imide tautomeric pair (form II);[11] sulfapyridine polymorphs exist only as the imide tautomer.[19] Other sulfonamides reported capable of exhibiting the imido tautomeric form in the crystal are sulfanilamide, sulfamethoxydiazine, sulfadoxine, sulfisoxazole, sulfathiazole, and sulfaguanidine.[19] For the crystalline polymorphs of the H-2 receptor antagonist, cimetidine, the intramolecular distances between the nitrogen atoms of the imidazole ring and the guanidine group have been calculated from x-ray diffraction data.[20] Also, the x-ray crystal analysis of the β-chloramphenicol palmitate polymorph has led to the hypothesis of a model of molecular packing within the crystal.[21]

THE SIGNIFICANCE OF POLYMORPHISM

As mentioned earlier, a change in crystal form could have an impact on the quality and performance of certain drug products. The degree of crystallinity; crystal habit, size, and size distribution; and the state of aggregation of drug particles can all affect bulk properties (e.g., mixing, filling, dusting) and pharmaceutical performance (e.g., dissolution, bioavailability, stability, suspendability, rheology).[22] To highlight the role of polymorphism in setting specifications for raw materials as well as processing parameters, the remainder of this article provides a variety of literature citations and examples.

Effects of Polymorphism on Dissolution Rate and Bioavailability. Dissolution rates of drugs are determined partly by crystal forms. Some polymorphs have identical dissolution rates, while others vary to a great extent. For example, the polymorphic pairs of both disopyramide[6] and mercaptopurine[7] and three of four polymorphs of tolbutamide[23] have been found to have similar dissolution rates, respectively. However, in other studies, polymorphs of acetohexamide,[24] chlorpropamide,[25] and phenylbutazone[26,27] displayed diverse dissolution rates. In a comparative study of the five phenylbutazone polymorphs, form C showed a maximum dissolution rate almost 55% higher than that of form A, while forms B and E displayed about 20 and 35% higher dissolution rates, respectively, than did form A; forms A and D were very similar in rates of dissolution.[26] Since dissolution rates may or may not reflect polymorphic variations, these

data alone should not be used as conclusive evidence of polymorphism.

Crystal formation can be controlled by choice of crystallization solvent or crystallization velocity. Most polymorphic preparations involve recrystallization techniques, but when a spray dryer is used, crystal velocity can be controlled.[28] When the drying temperature of the droplets sprayed from the atomizing nozzle is varied, metastable and amorphous forms (both high-energy because of their greater heats of solution) show greater dissolution rates than does the most stable form, unless there is an extremely rapid conversion to the stable form in the solvent medium.[8,29] Spray drying has been used to produce high-energy polymorphs or amorphous phases of carbromal,[30] chlorothiazide,[18] hydroflumethiazide,[31] phenobarbital,[30-32] phenylbutazone,[28,33] and sulfamethoxazole.[34] Also, freeze-drying has yielded amorphous phases of β-lactam antibiotics.[8]

Because the absorption of many drugs is dependent on their dissolution rates and solubility, polymorphism may be crucial to bioavailability—as classical studies with chloramphenicol have shown.[2,3] Again, however, polymorphism may or may not contribute to variations in absorption. The absorption characteristics of various polymorphs of disopyramide,[6] indomethacin,[35] and phenobarbital[36] have been shown to be very similar, but it has been postulated that variations in the toxicity of the antibiotic nystatin in mice are caused by the differing absorpiton rates of its various polymorphs.[37] (The LD_{50} values of of nystatin suspension used in the study varied between 23.2 and 635.4 mg/kg intraperitoneally, depending on the particular recrystallization technique.) In addition, the rates of absorption of sulfameter forms II and III in humans have been shown to differ (the ratio of form II to form III during the absorption phase was 1:30), although the extent of absorption, as indicated by 72-hour urinary excretion data, did not differ significantly.[38]

Effects of Processing on Crystal Form. Certain processing operations such as milling or compression can trigger a change in a drug product's crystal structure; therefore, it is important to consider the impact of a given processing operation on the crystal form, especially during scale-up. For example, compression studies involving 32 drugs known to exhibit polymorphism revealed that 11 of them were transformed under compression.[39] Specifically, caffeine, maprotiline hydrochloride, and sulfabenzamide all changed, to varying degrees, from unstable to stable polymorphic forms. In the tableting of caffeine, transformation from form A to form B increased drastically (about 20%) to a plateau as the applied pressure was increased (to about 300 MpA).

The heat and stress of the comminution process has been found to induce polymorphic transitions in aspirin,[40] clotrimazole,[41] digoxin,[17] methisazone,[42] phenobarbital,[43] phenylbutazone,[26,27,44,45] sulfamethoxydiazine,[46] sulfanilamide,[47,48] sulfathiazole,[49] and sulfaguanidine.[50]

Another example involves the antiviral agent methisazone, which is used in various formulations as a fine powder and has a tendency to revert to its original "fibrous" crystal form upon storage—a phenomenon that has been referred to as the growth of whiskers. Based on DTA, IR spectroscopy, and x-ray diffraction analysis, the unground and micronized forms have been found to represent two distinct polymorphic forms, the latter of which is the metastable form.[42]

Compression studies with aspirin,[40] meprobamate,[51] phenylbutazone,[44] and sulfathiazole[40,49] have also revealed that certain polymorphic forms are more suited to compression than others. In the case of phenylbutazone, for example, form A has been found to exhibit a higher Brinell hardness number (6.67 MNm^{-2}) than form B (3.63 MNm^{-2}),[44] which indicates form B's relative softness and ease of deformation compared with form A. In addition,

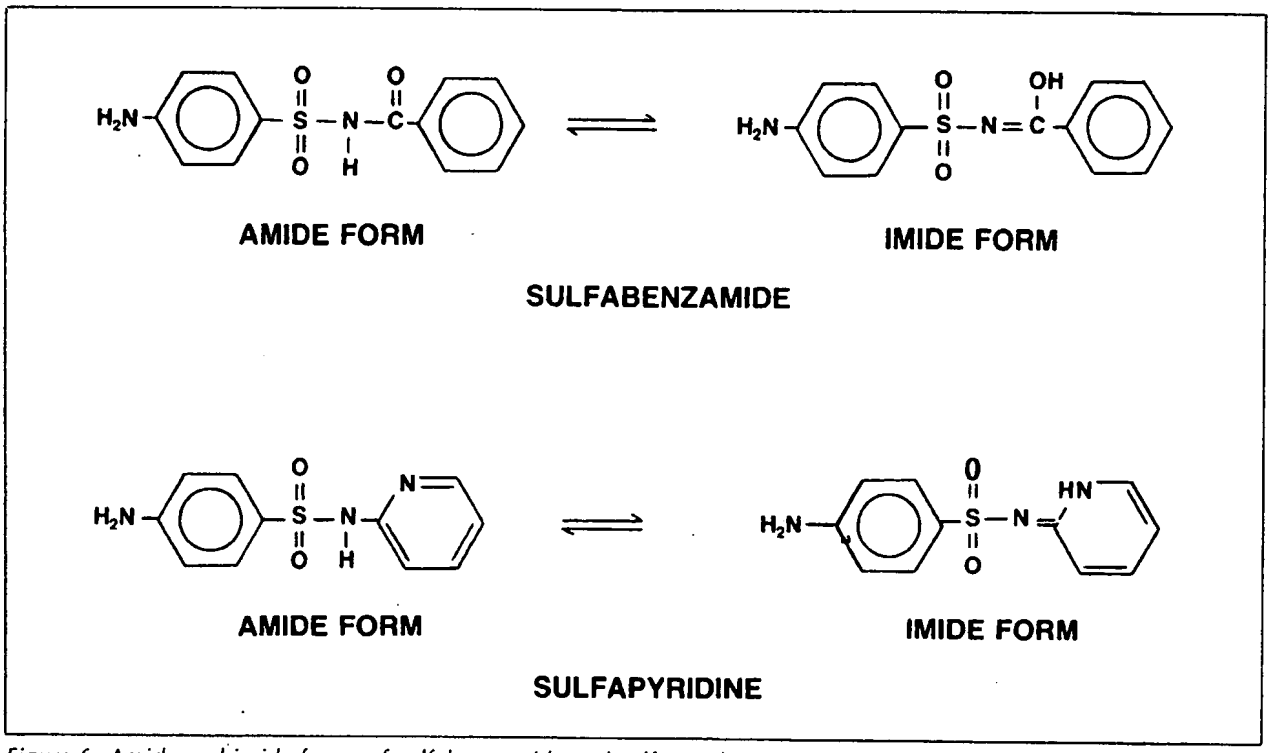


Figure 6: Amide and imide forms of sulfabenzamide and sulfapyridine.

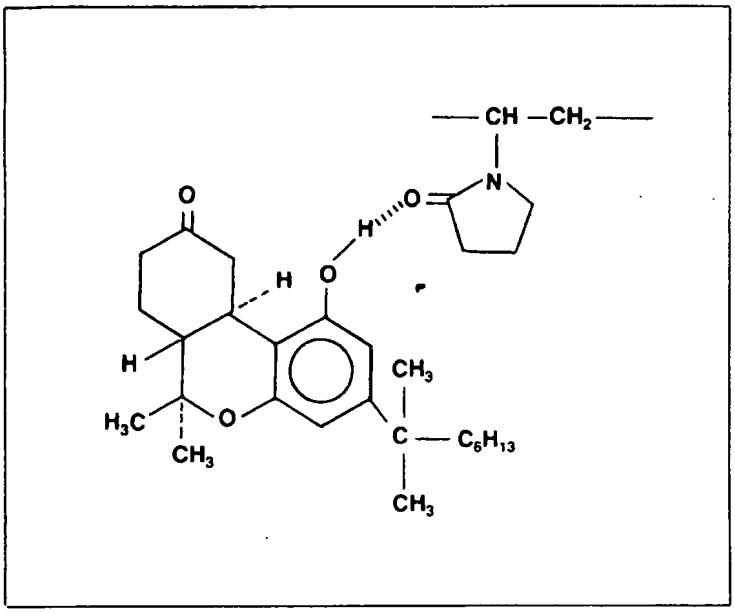


Figure 7: Presumed hydrogen bonding between nabilone, a synthetic cannabinoid, and povidine (PVP).

compression of phenylbutazone disks has been found to produce differences in surface characteristics, which were documented by photomicrography. The more-than-twofold difference in dissolution rates of crystal forms II and IV was attributed to the change in surface characteristics and crystal form.[45]

The Role of Excipients in Polymorphism. Excipients, vehicles, and other additives may have an effect on polymorphic stability; e.g., the transition of sulfamethoxazole to a semihydrate form has been found to be the reason for its instability in aqueous suspensions.[52] When used as additives, methyl cellulose, povidone (polyvinylpyrrolidone or PVP), and sucrose were found to inhibit this transition. On the other hand, carboxymethyl cellulose sodium enhanced the formation of the semihydrate. In other studies cellulose acetate phthalate[34,53] and talc[34] have been found to contribute to the polymorphism of spray-dried, microencapsulated sulfamethoxazole, while colloidal silica[34,53] and montmorillonite clay[34] were discovered to inhibit polymorphism but contribute to amorphism. In addition, it has been found that ointments of prednisolone are stabilized by certain polymorphs of long-chain alcohols, which retard hydrate formation.[54]

Another example of a polymorphic phenomenon in formulation studies involves the synthetic cannabinoid nabilone, an antiemetic.[55] A dry-dosage form of nabilone-starch was found to diminish in activity after several days. Upon extraction and thin-layer chromatographic analysis, however, nabilone was recovered intact. On investigation, it was found that two biologically active polymorphs of nabilone converted to a thermodynamically stable form upon grinding, exposure to heat, or extended storage. When the nabilone was reformulated by dispersion in a water-soluble matrix of PVP, it was found that the PVP-nabilone complex remained in an amorphous state, preventing transition and the resultant loss of activity. Presumably, the phenolic hydroxyl group of nabilone becomes hydrogen bonded to the amide carbonyl of PVP in the matrix as shown in Figure 7, and this bonding prevents the formation of the intermolecular hydrogen bonds necessary for the transition to the less-active crystal form.[55]

Other Polymorphic Studies. The accompanying box presents a compilation of recent polymorphic investigations of organic drugs that are currently on the market. The majority of the studies listed focus on the physicochemical aspects of the polymorphs, although a few stress bioavailability as well as pharmacological efficacy. Earlier literature, which was previously cited, covers the polymorphism of aspirin, chloramphenicol, erythromycin, insulin, meprobamate, novobiocin, and several other anticonvulsants, barbiturates, β-lactam antibiotics, sedatives, steroids, and sulfonamides.[1-3]

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REFERENCES

1. Biles JA, "Crystallography. Part I," *J Pharm Sci*, 51:499–509, 1962; "Crystallography. Part II," *J Pharm Sci*, 51:601–617, 1962.
2. Haleblian J, and McCrone W, "Pharmaceutical Applications of Polymorphism," *J Pharm Sci*, 58:911–929, 1969.
3. Haleblian JK, "Characterization of Habits and Crystalline Modifications of Solids and Their Pharmaceutical Applications," *J Pharm Sci*, 64:1269–1288, 1975.
4. Simmons DL, Ranz RJ, Picotte P, et al., "Polymorphism in Pharmaceuticals. 1. Chlordiazepoxide Hydrochloride," *Can J Pharm Sci*, 5:49–51, 1970.
5. Carstensen JT, *Solid Pharmaceutics: Mechanical Properties and Rate Phenomena*, New York, Academic Press, pp 14–19, 1980.
6. Gunning SR, Freeman M, and Stead JA, "Polymorphism of Disopyramide," *J Pharm Pharmacol*, 28:758–761, 1976.
7. Huang ML, and Niazi S, "Polymorphic and Dissolution Properties of Mercaptopurine," *J Pharm Sci*, 66:608–609, 1977.
8. Pikal MJ, Lukes AL, and Lang JE, "Quantitative Crystallinity Determinations for β-lactam Antibiotics by Solution Calorimetry: Correlations with Stability," *J Pharm Sci*, 67:767–772, 1978.
9. Lindenbaum S, and McGraw SE, "The Identification and Characterization of Polymorphism in Drugs by Solution Calorimetry," *Pharm Manufac*, 2(1):27–30, 1985.
10. Pakula R, Pichnej L, Spychala S, et al., "Polymorphism of Indomethacin. Part 1. Preparation of Polymorphic Forms of Indomethacin," *Pol J Pharmacol Pharm*, 29:151–156, 1977.

11. Rambaud J, Maury L, Lefebvre C, et al., "Physicochemical Study Comparing Sulfabenzamide Forms I and II," *Int J Pharm*, 15:199–212, 1983.
12. Muramatsu M, Iwahashi M, and Takenchi U, "Thermodynamic Relationship between α- and β-forms of Crystalline Progesterone," *J Pharm Sci*, 68:175–177, 1979.
13. Bellows JC, Chen FP, and Prasad PN, "Determination of Drug Polymorphs by Laser Raman Spectroscopy. 1. Ampicillin and Griseofulvin," *Drug Dev Ind Pharm*, 3:451–458, 1977.
14. Bolton BA, and Prasad PN, "Laser Raman Investigation of Pharmaceutical Solids: Griseofulvin and Its Solvates," *J Pharm Sci*, 70:789–793, 1981.
15. Leary JR, Dross SD, and Thomas NJK, "Characterization of the Polymorph of Tolbutamide," *Pharm Weekbl Sci Ed*, 3:62–66, 1981.
16. Guyer P, and Fritze D, "Dimorphism of Butacaine-Sulfate," *Arzneim Forsch*, 24:1978–1979, 1974.
17. Florence AT, and Salole EG, "Changes in Crystallinity and Solubility on Comminution of Digoxin and Observations on Spironolactone and Estradiol," *J Pharm Pharmacol*, 28:637–642, 1976.
18. Corrigan IO, Holohan EM, and Sabra K, "Amorphous Forms of Thiazide Diuretics Prepared by Spray Drying," *Int J Pharm*, 18:195–200, 1984.
19. Bar I, and Bernstein J, "Conformational Polymorphism VI: The Crystal and Molecular Structures of Form II, Form III, and Form V of 4-Amino-N-2-pyridinylbenzone-sulfonamide (Sulfapyridine)," *J Pharm Sci*, 74:255–263, 1985.
20. Shibata M, Kokuko H, Morimoto K, et al., "X-ray Structural Studies and Physicochemical Properties of Cimetidine Polymorphism," *J Pharm Sci*, 72:1436–1442, 1983.
21. Szulzewsky K, Kulpe S, Shulz B, et al., "Crystallographic Results on the Polymorphism of Chloramphenicol Palmitate," *Acta Pharm Suec*, 19:457–470, 1982.
22. Pfeiffer RR, Yang KS, and Tucker MA, "Crystal Pseudopolymorphism of Cephaloglycin and Cephalexin," *J Pharm Sci*, 59:1809–1814, 1970.
23. Al-Saieq SS, and Riley GS, "Polymorphism in Sulfonylurea Hypoglycemic Agents. Part 1. Tolbutamide," *Pharm Acta Helv*, 56:125–129, 1981.
24. Al-Saieq SS, and Riley GS, "Polymorphism in Sulfonylurea Hypoglycemic Agents. Part 3. Acetohexamide," *Pharm Acta Helv*, 57:43–46, 1982.
25. Al-Saieq SS, and Riley GS, "Polymorphism in Sulfonylurea Hypoglycemic Agents. Part 2. Chlorpropamide," *Pharm Acta Helv*, 57:8–11, 1982.
26. Tuladhar MD, Carless JE, and Summers MP, "Thermal Behavior and Dissolution Properties of Phenylbutazone Polymorphs," *J Pharm Pharmacol*, 35:208–214, 1983.
27. Matsunaga J, Nambu N, and Nagai T, "Physicochemical Approach to Biopharmaceutical Phenomena. XXX. Polymorphism of Phenylbutazone," *Chem Pharm Bull*, 24:1169–1172, 1976.
28. Matsuda Y, Kawaguchi S, Kobayashi H, et al., "Polymorphism of Phenylbutazone by a Spray Drying Method," *J Pharm Pharmacol*, 32:579–580, 1980.
29. Niazi S, "Effect of Polyethylene Glycol 4000 on Dissolution Properties of Sulfathiazole Polymorphs," *J Pharm Sci*, 65:302–304, 1976.
30. Junginger H, "Spray Drying Polymorphic Drugs. Part 1. Use of Spray Drying for Preparing Metastable Phases of Sedatives," *Pharm Ind*, 39:822–828, 1977.
31. Corrigan IO, Sabra K, and Holohan EM, "Physiochemical Properties of Spray-Dried Drugs: Phenobarbital and Hydroflumethiazide," *Drug Dev Ind Pharm*, 9:1–20, 1983.
32. Beyer C, "Spray Drying of Polymorphous Drugs with Phenobarbital as an Example. Part 1. Manufacture and Characteristics of Spray Products," *Acta Pharm Technol*, 24:171–174, 1978.
33. Matsuda Y, Kawaguchi S, Kobayashi H, et al., "Physicochemical Characterization of Spray-Dried Phenylbutazone Polymorphs," *J Pharm Sci*, 73:173–179, 1984.
34. Takenaka H, Kawashima Y, and Lin SY, "Polymorphism of Spray-Dried Microencapsulated Sulfamethoxazole with Cellulose Acetate Phthalate and Colloidal Silica, Montmorillonite, or Talc," *J Pharm Sci*, 70:1256–1260, 1981.
35. Yamamoto T, Yamamoto M, Nakae H, et al., "Pharmacokinetic Study by Gastrointestinal Absorption of Indomethacin Polymorphs in the Rabbit," *Yakugaku Zasshi*, 102:196–201, 1982.
36. Kato Y, and Watanabe F, "Relationship between Polymorphism and Bioavailability of Phenobarbital," *Yakugaku Zasshi*, 98:639–648, 1978.
37. Ghielmetti G, Bruzzee T, Bianchi C, et al., "Relationship between Acute Toxicity in Mice and Polymorphic Forms of Polyene Antibiotics," *J Pharm Sci*, 65:905–907, 1976.
38. Khalafallah N, Khalil SA, and Moustafa MA, "Bioavailability Determination of Two Crystal Forms of Sulfameter in Humans from Urinary Excretion Data," *J Pharm Sci*, 63:861–864, 1974.
39. Chan HK, and Doelker E, "Polymorphic Transformation of Some Drugs under Compression," *Drug Dev Ind Pharm*, 11:315–332, 1985.
40. Summers MP, Enever RP, and Carless JE, "The Influence of Crystal Form on the Radial Stress Transmission Characteristics of Pharmaceutical Materials," *J Pharm Pharmacol*, 28:89–99, 1976.
41. Borka L, and Valdimarsdottir S, "Polymorphism of Azaperone and Clotrimazole," *Acta Pharm Suec*, 12:479–484, 1975.
42. Lee KC, and Hershey JA, "Crystal Modifications of Methisazone by Grinding," *J Pharm Pharmacol*, 29:249–250, 1977.
43. Riley GS, "Characterization of Phenobarbitone Samples," *J Pharm Pharmacol*, 25:919–920, 1974.
44. Tuladhar MD, Carless JE, and Summers MP, "Effects of Polymorphism, Particle Size, and Compression Pressure on the Dissolution Rate of Phenylbutazone Tablets," *J Pharm Pharmacol*, 35:269–274, 1983.
45. Ibrahim HG, Pisano F, and Bruno A, "Polymorphism of Phenylbutazone: Properties and Compressional Behavior of Crystals," *J Pharm Sci*, 66:669–673, 1977.
46. Giordano F, Bettinetti GP, Caramella C, et al., "Effect of Comminution on the Transition Phases of Polymorphic Modifications of Sulfamethoxydiazine," *Boll Chim Farm*, 116:433–438, 1977.
47. Junginger H, "Changes in Polymorphic Modifications Caused by Mechanical Treatment. Part 2," *Dtsch Apotheker-Ztg*, 116:1880–1883, 1976; "Changes in Polymorphic Modifications Caused by Mechanical Treatment. Part 3," *Dtsch Apotheker-Ztg*, 117:456–459, 1977.
48. Cruaud O, Puchene D, Puisieux F, et al., "Study of Polymorphous Transformation of Sulfanilamide during Tablet Manufacture," *J Pharm Belg*, 36:15–20, 1981.
49. Kala H, Moldenhauer H, Giese R, et al., "On the Polymorphism of Sulfathiazole and Its Crystallographic Behavior under Compression Pressure," *Pharmazie*, 36:833–838, 1981.
50. Masse J, Chauret A, Salin JP, et al., "Study of Polymorphic Transformations of Sulfaguanidine during Compression," *Thermochim Acta*, 40:377–387, 1980.
51. Burger A, Ramberger R, and Schmidt W, "The Influence of Polymorphism of the Active Substance on the Properties of Tablet. Part 3: Compressional Behavior of Meprobamate," *Pharmazie*, 36:41–46, 1981.
52. Graf E, Beyer C, and Abdallah O, "Physical Instability of Sulfamethoxazole Aqueous Suspensions," *Pharm Ind*, 44:1071–1074, 1982.
53. Kawashima Y, Lin SY, and Takenaka H, "Polymorphism and Drug Release Behavior of Spray-Dried Microcapsules of Sulfamethoxazole with Polysaccharide Gum and Colloidal Silica," *Drug Dev Ind Pharm*, 9:1445–1463, 1983.
54. Kaiho F, Takigawa Y, Ando A, et al., "Effects of Long-Chain Alcohols on Conversion of Prednisolone Crystals in Oil in Water Type Ointments," *Yakugaku Zasshi*, 99:1068–1072, 1979.
55. Thakkar AL, Hirsch CA, and Page JG, "Solid Dispersion Approach for Overcoming Bioavailability Problems Due to Polymorphism of Nabilone, a Cannabinoid Derivative," *J Pharm Pharmacol*, 29:783–784, 1977.
56. Burger A, and Ramberger R, "On the Polymorphism of Pharmaceuticals and Other Molecular Crystals. I. Applicability of Thermodynamic Rules," *Mikrochim Acta*, 1:273–316, 1979.
57. Graf E, Beyer C, and Abdallah O, "Polymorphism of Acetohexamide. Part 1. Preparation and Properties of Modifications," *Acta Pharm Technol*, 25:9–20, 1979.
58. Graf E, Beyer C, and Abdallah O, "Coprecipitates of Acetohexamide," *Acta Pharm Technol*, 28:225–230, 1982.
59. Girgis-Takla P, and Chroneos J, "Polymorphism of Acetohexamide," *J Pharm Pharmacol*, 29:640–642, 1977.
60. Yokoyama T, Umeda T, Konishi A, et al., "Identification of Polymorphs of Tolbutamide, Acetohexamide, and Chlorpropamide by the Polarizing Microscope," *Yakuzaigaku*, 38:229–232, 1978.
61. Jersler B, and Lund U, "Organic Solid Phase Analysis. Part 1. Alleged Polymorphism of Acetylsalicylic Acid," *Arch Pharm Chem Sci Ed*, 9:61–69, 1981.
62. Nikolics K, Bidlo G, and Nikolics K, "Contribution to the Polymorphism of Barbiturates Due to Solvents," *Acta Pharm Hung*, 44:133–139, 1974.

63. Rodriquez-Galan IC, Galan AC, and Ruiz JA, "Contribution to the Study of Polymorphism of Barbiturates. Part 1. Characterization of the Pseudopolymorph Forms of Amobarbital Sodium," *Cienc Ind Farm*, 11:125–136, 1979.
64. Azibi M, Draguet-Brughmans M, and Bouche R, "Polymorphism of Butyrophenones: Azaperone and Fluanisone," *Pharm Acta Helv*, 56:190–193, 1981.
65. Kuhnert-Brandstatter M, and Wurian I, "Thermoanalytical and IR Spectroscopical Investigations on Enantiomeric Polymorphs of Drugs. Part 1," *Sci Pharm*, 50:3–11, 1982.
66. Azibi M, Draguet-Brughmans M, and Bouche R, "Polymorphism of Butyrophenones: Benperidol and Droperidol," *Pharm Acta Helv*, 57:182–188, 1982.
67. Perrier R, Chauvet A, and Masse J, "Thermoanalytical Study of Some Steroids. II. Cortisone Derivatives," *Thermochim Acta*, 44:189–201, 1981.
68. Draguet-Brughmans M, Draux P, and Bouche R, "Polymorphism of Butabarbital," *J Pharm Belg*, 36:397–403, 1981.
69. Sabon F, Alberola S, Terol A, et al., "Polymorphism and Solubility of Caffeine," *Trav Sco Pharm Montpellier*, 39:19–24, 1979.
70. Kalizan R, and Hac E, "Studies on the Polymorphism of Carbromal," *Pharmazie*, 31:453–456, 1976.
71. Gatlin L, and Deluca PP, "Study of the Phase Transitions in Frozen Antibiotic Solutions by Differential Scanning Calorimetry," *J Paren Sci Technol*, 34:398–408, 1980.
72. Otsuka M, and Kaneniwa N, "Hygroscopicity of Cephalexin Crystals," *Yakugaku Zasshi*, 102:359–364, 1982.
73. Burger A, "New Investigative Results on the Polymorphism of Chloramphenicol Palmitate," *Sci Pharm*, 45:269–281, 1977.
74. Andersgood H, Finholt P, Gjermundsen R, et al., "Rate Studies on Dissolution and Enzymatic Hydrolysis of Chloramphenicol Palmitate," *Acta Pharm Suec*, 11:239–248, 1974.
75. Yamamoto K, Matsuda S, Nakomo M, et al., "Physiochemical Properties and Intestinal Absorption of a Ground Mixture of Chloramphenicol Palmitate with Microcrystalline Cellulose," *Yakugaku Zasshi*, 97:367–372, 1977.
76. Cameroni R, Coppi G, Forni F, et al., "Physical Properties and Bioavailability of Chloramphenicol Palmitate in a Mixture Formulated with Microcrystalline Cellulose," *Farmaco Ed Prat*, 39:76–86, 1984.
77. Bernabei MT, Forni F, Coppi G, et al., "Crystallinity and Equivalence of Chloramphenicol Palmitate," *Farmaco Ed Prat*, 38:391–402, 1983.
78. Van Aerde P, Remon JP, DeRudder D, et al., "Polymorphic Behavior of Chloroquine Diphosphate," *J Pharm Pharmacol*, 36:190–191, 1984.
79. O'Driscoll KM, and Corrigan IO, "Chlorothiazide-Polyvinylpyrrolidone (PVP) Interactions: Influence on Membrane Permeation (Everted Rat Intestine) and Dissolution," *Drug Dev Ind Pharm*, 8:547–564, 1982.
80. Burger A, "Polymorphism of Oral Antidiabetics. Part 3. Chlorpropamide," *Sci Pharm*, 43:152–161, 1975.
81. Ebian AR, and El-Gindy NA, "Codeine Crystal Forms. I. Preparation, Identification, and Characterization," *Sci Pharm*, 46:1–7, 1978.
82. Laine E, Tuominen V, Jalonen H, et al., "Effect of Storage Conditions on Structure of Cyclophosphamide," *Acta Pharm Fenn*, 92:243–248, 1983.
83. Kuhnert-Brandstatter M, and Moser I, "Polymorphism of Dapsone and Ethambutol Dihydrochloride," *Mikrochim Acta*, 1:125–136, 1979.
84. Walking WD, Almond H, Paragamian V, et al., "Difenoxin Hydrochloride Polymorphism," *Int J Pharm*, 4:39–46, 1979.
85. Chiou WL, and Kyle LE, "Differential Thermal, Solubility, and Aging Studies on Various Sources of Digoxin and Digitoxin Powder: Biopharmaceutical Implications," *J Pharm Sci*, 68: 1224–1229, 1979.
86. Nurnberg E, and Dolle B, "Identification of Paracrystalline Modifications of Digoxin," *Acta Pharm Technol*, 29:75–83, 1983.
87. Nurnberg E, and Dolle B, "Occurrence of Paracrystalline Forms, Demonstrated for Digoxin," *Acta Pharm Technol*, 29:1–8, 1983.
88. Kuhnert-Brandstatter M, Wurian I, and Geiller M, "Thermoanalytical and IR Spectroscopic Studies on Enantiotropic Polymorphs of Drugs III," *Sci Pharm*, 50:208–216, 1982.
89. Pelizza G, Nebuloni M, and Gallo GG, "Polymorphism of Erythromycin Studied by DTA," *Farmaco Ed Sci*, 31:254–263, 1976.
90. Picolo J, and Sakr A, "Influence of Crystalline State and Particle Size on the Dissolution Rate of Erythromycin Estolate," *Pharm Ind*, 46:1277–1279, 1984.
91. Kuhnert-Brandstatter M, and Winkler A, "Thermoanalytical and IR Spectroscopic Studies on Several Crystal Forms of Estradiol and Androstane Type Drugs," *Sci Pharm*, 44:177–190, 1976.
92. Ebian AR, Khalil SA, Moustafa MA, et al., "Polymorphism and Solvation of Ethinyl Estradiol," *Pharm Acta Helv*, 54:111–114, 1979.
93. Cameroni R, Gamberini G, Ferioli V, et al., "Polymorphism of Ethyl Biscoumacetate," *Farmaco Ed Prat*, 32:125–138, 1977.
94. Mascellani G, and Scapini G, "Purification of Flucloxacillin through Pseudopolymorphic Crystalline Forms," *Farmaco Ed Prat*, 30:555–561, 1975.
95. Burger A, and Ramberger R, "Thermodynamic Relationships between Polymorphic Modifications: Flufenamic Acid and Mefenamic Acid," *Mikrochim Acta*, 1:17–28, 1980.
96. Kuhnert-Brandstatter M, Borka L, and Friedrick-Sander G, "Polymorphism of Drugs Flufenamic Acid and BL 191," *Arch Pharm*, 307:845–853, 1974.
97. Burger A, "Polymorphism of Oral Antidiabetics. Part 3. Glymidine Sodium," *Sci Pharm*, 44:107–118, 1976.
98. Kuhnert-Brandstatter M, and Heindel W, "Polymorphism of Homatropine Hydrochloride," *Sci Pharm*, 43:112–116, 1975.
99. Merkle HP, "Examination of Polyvinylpyrrolidone-Drug Coprecipitate Dissolution," *Acta Pharm Technol*, 27:193–203, 1981.
100. Chrai SS, and Stupak EI, "Sterile Micronized Hydrocortisone—A Simple Method for Preparation," *Bull Parent Drug Assoc*, 30:100–103, 1976.
101. Yokoyama T, Umeda T, Kuroda K, et al., "Studies on Drug Nonequivalence. 9. Relationship between Polymorphism and Rectal Absorption of Indomethacin," *Yakugaku Zasshi*, 99:837–842, 1979.
102. Borka L, "Polymorphism of Indomethacin. New Modifications, Their Melting Behavior and Solubility," *Acta Pharm Suec*, 11:295–303, 1974.
103. Ford JL, and Rubenstein MH, "Aging of Indomethacin—Polyethylene Glycol 6000 Solid Dispersion," *Pharm Acta Helv*, 54:353–358, 1979.
104. Kuhnert-Brandstatter M, and Bosch L, "Polymorphism of Drugs: Medrogesterone, Phensuximide, and Prothioamide," *Arch Pharm*, 311:757–761, 1978.
105. Burger A, Schulte K, and Ramberger R, "Polymorphic Drugs of the European Pharmacopeia. I: IR Spectroscopic and Thermodynamic Studies of Three Polymorphs of Meprobamate," *Arch Pharm*, 314:398–408, 1981.
106. Clements JA, and Popli SD, "Preparation and Properties of Crystal Modifications of Meprobamate," *Can J Pharm Sci*, 8:88–92, 1973.
107. Burger A, "Polymorphs of Oral Antidiabetic Drugs. Part 5. Metahexamide: Forms, Modifications, and a Hydrate," *Sci Pharm*, 47:16–25, 1979.
108. Gharavi M, and James KC, "Properties of Testosterone and Related Androgens Crystallized from Normal Alkanols," *Int J Pharm*, 14:325–331, 1983.
109. Hoelgaard A, and Moller N, "Hydrate Formation of Metronidazole Benzoate in Aqueous Suspensions," *Int J Pharm*, 15:213–221, 1983.
110. Fabregas JL, and Beneyto JE, "Crystalline Forms of Nicergolline," *Farmaco Ed Prat*, 36:256–261, 1981.
111. Eckert T, and Mueller J, "Polymorphic Modifications of Nifedipine from Supercooled Melts," *Arch Pharm*, 310:116–118, 1977.
112. Vidler JAG, "Occurrence of Two Polymorphs of D-Penicillamine," *J Pharm Pharmacol*, 28:663, 1976.
113. Draguet-Brughmans M, Bouche R, Flandre JP, et al., "Polymorphism and Bioavailability of Pentobarbital," *Pharm Acta Helv*, 54:140–145, 1979.
114. Bosly J, Lapierce CL, and Bouche R, "Dimorphism of Phenobarbital Sodium," *J Pharm Belg*, 36:249–250, 1981.
115. Chauvet A, and Masse J, "Thermic Behavior of Phenylbutazone," *Trav Soc Pharm Montpellier*, 38:31–42, 1978.
116. Muller BW, "Polymorphism of Nonsteroidal Antiinflammatory Drugs. Part 1. Polymorphism and Pseudopolymorphism of Phenylbutazone," *Pharm Acta Helv*, 53:333–340, 1978.
117. Chakrabarti S, Van Severen R, and Braeckman P, "Studies on the Crystalline Form of Phenytoin," *Pharmazie*, 33:338–339, 1978.
118. Bernabei MT, Gamberini G, and Cameroni R, "Polymorphism of Progesterone. Part 3," *Farmaco Ed Prat*, 29:184–191, 1974.
119. Bernabei MT, Gamberini G, Ferioli V, et al., "Polymorphic Forms of Progesterone Dispersed in a Polydimethylsiloxane Elastomer," *Boll Chim Farm*, 121:347–353, 1982.
120. Borka L, "Polymorphism of Propantheline Bromide," *Acta Pharm Suec*, 20:155–157, 1983.

121. Muller BW, and Beer Y, "Polymorphism and Changes of Propyphenazone," *Acta Pharm Technol*, 28:97–102, 1982.
122. Pelizza G, Nebuloni M, Ferrari P, et al., "Polymorphism of Rifampicin," *Farmaco Ed Prat*, 32:471–481, 1977.
123. El-Dalsh SS, El-Sayed AA, Badawi AA, et al., "Studies on Spironolactone Polymorphic Forms," *Drug Dev Ind Pharm*, 9:877–894, 1983.
124. Moustafa MA, Khalil SA, Ebian AR, et al., "Succinylsulfathiazole Crystal Forms. Part I," *J Pharm Sci*, 63:1103–1109, 1974; "Part 2," *J Pharm Sci*, 64:1481–1484, 1975; "Part 3," *J Pharm Sci*, 64:1485–1489, 1975.
125. Sabon F, Alberola S, Terol A, et al., "Polymorphism and Solubility of Sulfabenzamide," *Trav Soc Pharm Montpellier*, 39:43–47, 1979.
126. Burger A, Ramberger R, and Schulte K, "Analysis of the Polymorphous System of Sulfamethoxydiazine," *Arch Pharm*, 313:1020–1028, 1980.
127. Comte U, Colombo P, Caramella C, et al., "On the Direct Compression of Sulfamethoxydiazine Polymorphic Forms: Part I," *Farmaco Ed Prat*, 30:194–206, 1975.
128. Hadi IA, Mezoji J, Kedressy G, et al., "Biopharmaceutical Studies on Sulfadimidine Modifications," *Pharmazie*, 32:791–793, 1977.
129. Lin HO, Baenziger NC, and Guillory JK, "Physical Properties of Four Forms of Sulfanilamide. I. Densities, Refractive Indexes, and X-ray Diffraction Measurements," *J Pharm Sci*, 63:145–146, 1974.
130. Bulenkov TI, Upsenskaya SI, Popkov VA, et al., "Preparation and Characteristics of Some Streptocide Modifications," *Farmatsiya*, 28:2428, 1979.
131. Burger A, Schulte K, and Ramberger R, "Explanation of Thermodynamic Relationships among Five Polymorphic Modifications of Sulfapyridine by Using DSC," *J Therm Anal*, 19:475–484, 1980.
132. Gouda MW, Ebian AR, Moustafa MA, et al., "Sulfapyridine Crystal Forms," *Drug Dev Ind Pharm*, 3:273–290, 1977.
133. Lagas M, and Lerk CF, "Polymorphism of Sulfathiazole," *Int J Pharm*, 8:11–24, 1981.
134. Burger A, and Dialer RD, "New Investigational Results of Sulfathiazole Polymorphism," *Pharm Acta Helv*, 58:72–78, 1983.
135. Kalizan R, "Analytical Studies on Crystals of Theophylline Obtained at Various Conditions," *Pharm Acta Helv*, 51:159–160, 1976.
136. Burger A, "Polymorphism of Oral Antidiabetics. Part 2. Tolbutamide," *Sci Pharm*, 43:161–168, 1975.
137. Dommeyer A, Boucherat J, and Buri P, "Relationship between Physicochemical Properties of Tolbutamide-Polyvinylpyrrolidone Coprecipitates and Dissolution Characteristics," *Acta Pharm Technol*, 27:205–210, 1981.
138. Borka L, "Polymorphism of Triamcinolone Diacetate," *Int J Pharm*, 16:93–96, 1983.
139. Bettinetti GP, Giordano F, and Ferloni P, "Thermal Behavior of Trimethoprim and Some Trimethoprim Compounds," *Farmaco Ed Sci*, 35:706–714, 1980.
140. Bettinetti GP, Giordano F, LaManna A, et al., "Polymorphs of Trimethoprim. Part I," *Boll Chim Farm*, 117:522–529, 1978; "Part 2," *Boll Chim Farm*, 117:596–604, 1978.
141. Bettinetti GP, Giordano F, LaManna A, et al., "Trimethoprim Crystal Forms," *J Pharm Pharmacol*, 28:87–88, 1976. □

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